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Mixed-ligand complexes of yttrium-90 dialkyldithiocarbamates with 1,10-phenanthroline as a possible agent for therapy of hepatocellular carcinoma

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ABSTRACT

Yttrium-90 is a radioelement which has found wide use in targeted radionuclide therapy because of its attractive physical and chemical properties. Radioembolisation of hepatocellular carcinoma with radiolabelled Lipiodol is a method of choice. We have synthesised a series of alkyldithiocarbamate yttrium complexes, easily extracted into Lipiodol due to their high lipophilicity. Among the prepared series, a new radioconjugate, which is stable over an extended period of time, has been prepared, and could represent a potential treatment procedure for hepatocellular carcinoma.

Keywords: Dithiocarbamate; 1,10-phenanthroline; Hepatocellular carcinoma; Lipiodol; Radionuclide therapy; Yttrium-90

1- Introduction

Hepatocellular carcinoma (HCC), the most common form of primary liver cancers, is the fifth most common tumour worldwide, and even ranks third in terms of mortality (Ferlay et al., 2010; Jemal et al., 2011). For the vast majority of patients not eligible to curative treatments, such as resection or transplantation, there is a wide range of palliative treatments which can be proposed, among which are chemoembolisation and radioembolisation with Lipiodol or microspheres (Venook, 1994; Thomas and Zhu, 2005; Liapi and Geschwind, 2010; Lencioni, 2010; Raoul et al., 2010). Lipiodol is an oily medium which has shown to be selectively retained in tumour when administered intra-arterially (Chou et al., 1995). Lipiodol has been labelled with iodine-131 (Liebster and Kocandrle, 1964; Raoul et al., 1986), rhenium-188 (Lepareur et al., 2008), yttrium-90 (Wang et al., 1996b; Yu et al., 2003), and radiolanthanides (Das et al., 2009; Subramanian et al., 2010). Yttrium-90 (pure beta-emitter, $E_{\beta_{\max}} = 2.27$ MeV, $t_{1/2} = 64$ h, max tissue penetration = 12 mm) has ideal properties for targeted radiotherapy, and has found wide use in peptide receptor radionuclide therapy (Goffredo et al., 2011), radioimmunotherapy (Sharkey et al., 2010) and radioembolisation (Salem and Hunter, 2006). It has been suggested as a suitable isotope to label Lipiodol as it should lead to a significantly reduced whole-body dose compared to ^{131}I -Lipiodol, since more than 90 % of this dose is due to the emitted gamma rays (respectively 0.02 rad/mCi compared to 1.9 rad/mCi, based on estimated dosimetry) (Madsen et al., 1988). After having successfully developed radiolabelled Lipiodol with rhenium-188 (Lepareur et al., 2004; Lepareur et al., 2012), we decided to develop a new labelling of Lipiodol with yttrium-90 for the treatment of HCC, as a complementary tool in the treatment armamentarium. A series of heteroligand yttrium dialkyldithiocarbamate complexes with 1,10-phenanthroline has been prepared, and their suitability to label Lipiodol has been investigated.

2- Experimental

2.1. Materials and Methods

Yttrium-90 was obtained from IBA as yttrium chloride in HCl 0.04 M (Ytracis, CIS bio International/IBA, Gif-sur-Yvette, France). Lipiodol was obtained from Guerbet (Villepinte, France). 1,10-Phenanthroline was purchased from Acros (Illkirch, France). Sodium diethyldithiocarbamate was purchased from Aldrich (Saint Quentin Fallavier, France). Other dithiocarbamates were synthesised according to the literature from the corresponding secondary amines and carbon disulfide. Briefly, in a 100 mL round-bottom flask, under nitrogen, 14 mmol of *N*-methylalkylamine were diluted in 30 mL diethyl ether. The round-bottom flask was cooled down to -15°C in an ice/salt bath. 532 mg (13.3 mmol) of sodium hydroxide in methanol were added under stirring. 1.1 g (14.6 mmol) of carbon disulfide were slowly added under stirring. The mixture was stirred for 30 minutes in the ice/salt bath, then at room temperature for 90 minutes. The obtained precipitate was filtered then dried under vacuum to give a white powder.

Non-radioactive compounds were characterized by ^1H and ^{13}C NMR recorded with a BRUKER ARX 400 (Billerica MA, USA) at 400.13 and 100.62 MHz, respectively, in CDCl_3 , calibrated internally to the residual solvent. ES mass analysis was done on a Shimadzu LCMS 2020 (Kyoto, Japan). Activity measurements were done in a CRC-127R well-counter (Capintec Inc., Ramsey NJ, USA). TLC analyses were done on ITLC-SG plates (Pall Life Sciences, Ann Arbor MI, USA) with methanol as mobile phase. The plates were analysed with a Perkin Elmer Cyclone Storage Phosphor Imager, using the Packard Optiquant v04.00 software.

2.2. Preparation of [$^{89}\text{Y}(\text{DEDC})_3(\text{Phen})$] (**C1**)

MW = 713

In a 20 mL round-bottom flask, under nitrogen, 180 mg (1 mmol) of 1,10-phenanthroline, dissolved in 2 mL methanol, and 675 mg (3 mmol) of sodium *N,N*-diethyldithiocarbamate trihydrate, dissolved in 2 mL methanol, are placed. 200 mg (1 mmol) of yttrium chloride were dissolved in 2 mL methanol and were added dropwise to the ligands. The complex precipitated. The mixture was stirred for 20 minutes at room temperature then filtered, washed with methanol, and dried under vacuum to give **C1** as white crystals (619 mg, 87 %). ^1H NMR (CDCl_3): 9.99 (dd, $J = 4.9, 1.5$ Hz, 2H, H-Phen), 8.37 (dd, $J = 8.1, 1.6$ Hz, 2H, H-Phen), 7.85 (s, 2H, H_4), 7.72 (dd, $J = 8.1, 4.9$ Hz, 2H, H-Phen), 3.83 (q, $J = 7.1$ Hz, 12H, NCH_2), 1.12 (t, $J = 7.1$ Hz, 18H, CH_3). ^{13}C NMR (CDCl_3): 205.8 (CS_2), 151.8 (CH-Phen), 144.9 (C-Phen), 137.9 (CH-Phen), 129.4 (C-Phen), 126.8 (CH-Phen), 123.5 (CH-Phen), 46.1 (NCH_2), 12.4 (CH_3). $m/z = 713.40$. $R_f(\text{MeOH}) = 0.76$.

2.3. Preparation of [$^{90}\text{Y}(\text{dte})_3(\text{Phen})$] and Lipiodol radiolabelling

100 μL of $^{90}\text{YCl}_3$ in acetate buffer (pH = 4.75) were added to a solution of 100 μL of sodium dithiocarbamate $15 \cdot 10^{-2}$ M in ethanol and 100 μL of phenanthroline $5 \cdot 10^{-2}$ M in ethanol. Several parameters such as concentration of ligands, volume and pH of the reaction mixture, incubation time, and temperature were varied extensively to arrive at the optimised protocol. For the preparation of ^{90}Y -Lipiodol, [$^{90}\text{Y}(\text{dte})_3(\text{Phen})$] complex prepared under optimised reaction conditions was extracted in 2 mL Lipiodol. After vigorous shaking for 2 minutes to ensure homogeneous dispersion of the complex in Lipiodol, the phases were separated by centrifugation. Chemical identity of the radiotracer was assessed for [$^{90}\text{Y}(\text{DEDC})_3(\text{Phen})$] by comparing its TLC profile in MeOH with that of the fully characterised analogous non-

radioactive complex C1. Other dithiocarbamates tracers were assumed to have similar structures.

2.4. Determination of complexation yield of [$^{90}\text{Y}(\text{dthc})_3(\text{Phen})$]

The complexation yield of the [$^{90}\text{Y}(\text{dthc})_3(\text{Phen})$] radiotracer prepared was determined by solvent extraction technique. 300 μL of chloroform were added. The mixture was vigorously shaken, then centrifuged (3840 rpm, 15 min) to separate the phases. The two phases were carefully collected and counted in a well-counter. The complexation yield was determined as the organic layer activity on the total (aqueous + organic) activity.

2.5. Determination of labelling yield of Lipiodol

The labelling yield of Lipiodol was determined by an analogue technique. 900 μL of saline and 2 mL of Lipiodol were added. The mixture was vigorously shaken, and then centrifuged (3840 rpm, 15 min) to separate the phases. The two phases were carefully collected and counted in a well-counter. The complexation yield was determined as the Lipiodol layer activity on the total (aqueous + Lipiodol) activity.

2.6. *In vitro* stability of ^{90}Y -Lipiodol

To check the *in vitro* stability of ^{90}Y -labelled Lipiodol, 2 mL of saline was added to the preparation and mixed vigorously. The mixture was allowed to settle at room temperature. 100 μL of aliquots were withdrawn from both layers at different time intervals post-preparation and the associated activity was counted. The stability of the radiolabelled preparation at various time points was determined by calculating the percentage of activity associated with the lipid phase from these data.

3- Results and Discussion

When injected through the hepatic artery, Lipiodol, an iodinated mixture of esterified poppyseed oil, is selectively trapped in tumour cells (HCC and some hepatic metastases) (Nakakuma et al., 1985). Besides, Lipiodol displays a prolonged retention within the tumour, while it is more quickly cleared from the healthy liver (Chou et al, 1995; Kan, 1996). It has thus been used for the detection of HCC and as a vector for chemotherapeutic drugs (Bhattacharya and Dusheiko, 1995; Dalla Palma, 1998).

When radiolabelled with iodine-131, Lipiodol has shown a high tumour-to-liver ratio, with some activity in the lungs (depending on arteriovenous shunts) and no activity in the thyroid, thus excluding iodine-131 release (Madsen et al., 1988; Raoul et al., 1988; Yoo et al., 1994). Covalently labelled Lipiodol with rhenium-188 and yttrium-90 demonstrated a biodistribution similar to ^{131}I -Lipiodol (Wang et al., 1996a; Wang, et al., 1996b). This approach was however disappointing, and it was demonstrated that solubilisation of a labelled lipophilic chelate into Lipiodol was a better approach (Jackson et al., 2000). To efficiently interact with Lipiodol, the radiocomplex has to be conveniently lipophilic. Other important criteria when choosing which ligands to use are ease of labelling and, as much as possible, known toxicity and compatibility for *in vivo* use (to facilitate acceptance for human use). One type of ligands that fits these criteria is dialkyldithiocarbamates (dtc). Lipophilicity can easily be modified by modulating the length of the alkyl chain. Several radiopharmaceutical complexes have been described with dithiocarbamates, with indium-113m (Abram et al., 1985), copper-62 (Matsumoto et al., 1990), bismuth-212 (Parks et al., 1992), technetium-99m (Pasqualini et al., 1994), and rhenium-188 (Boschi et al., 2004). Moreover, rare earth complexes with dithiocarbamates have been the subject of an abundant literature and their structures have been extensively discussed (Nief, 1998; Cotton, 2004; Hitchcock et al., 2004; Regulacio et al., 2005). Reaction of yttrium and lanthanides with dithiocarbamates can results in ternary

neutral complexes or quaternary anionic complexes. In the first case, lanthanides favouring octa-coordinated structure, the coordination sphere of the metal is usually completed with solvents molecules, such as $[\text{Ln}(\text{Me}_2\text{dtc})_3(\text{DMSO})_2]$ ($\text{Ln} = \text{La}, \text{Pr}, \text{Nd}, \text{Sm-Tb}$) (Su et al., 1995) or $[\text{Ln}(\text{Me}_2\text{dtc})_3(\text{THF})_2]$ ($\text{Ln} = \text{Ce}, \text{Nd}, \text{Tb}$) (Hitchcock et al., 2004), or else with the addition of a neutral π -donor ligand such as 2,2'-bipyridyl or 1,10-phenanthroline (Su et al., 1996; Regulacio et al., 2008). With this additional ligand, there is an easy electron delocalisation among the large conjugate system which, as well as the rigid plane, enables a stable crystal packing, thus enhances the stability of the complex (Su et al., 1999). Mixed dithiocarbamate-phenanthroline yttrium and lanthanide complexes are easily synthesised in soft conditions, readily crystallize and are air-stable. Some may even be prepared in aqueous media (Ivanov et al., 2002). This can be advantageous for the preparation of radiotracers. On the contrary, without the neutral bidentate ligand, complexes of the $[\text{Ln}(\text{dtc})_3]$ type are unstable and hydrolyze rapidly, necessitating inert atmosphere and strongly anhydrous conditions (Brown and Holah, 1968). Therefore, 1,10-phenanthroline was chosen to complete the coordination sphere of the yttrium complexes.

Important factors for the optimal radiolabelling of the ^{90}Y -radiotracer are the solvent, volume, temperature, incubation time and concentration of the components. Their effects were thus studied. Ligands with different alkyl chain lengths were also investigated. It appeared that the lower was the volume, the higher was the reaction yield. EtOH was chosen to dissolve the ligands, as it is the most compatible solvent for human injection. Concentrations of the ligands were varied from 10^{-3} to 10^{-1} M – with a 3:1 ratio for dtc:Phen – to ascertain the optimum ligand concentration required for maximum complexation. It was found that $15 \cdot 10^{-2}$ M for dithiocarbamate and $5 \cdot 10^{-2}$ M for 1,10-phenanthroline gave the best results.

Concerning the pH of the reaction medium, a slightly acidic pH was found to give the best results (Figure 2). In neutral to basic pH, yttrium chloride quickly hydrolyses to insoluble $Y(OH)_3$, thus preventing the reaction to proceed correctly. When the reaction medium was too acidic, the reaction did not proceed as well, because the dithiocarbamate is under the dithiocarbamic acid form (*i.e.* pKa of the diethyldithiocarbamic acid/diethyldithiocarbamate couple is 3.37 (Aspila et al., 1970)) which cannot bind to the metal. The reaction thus proceeded in ammonium acetate buffer (pH = 4.75).

Temperature and reaction time were also investigated, with the DEDC ligand, and it was demonstrated that room temperature gave the best results (Figure 3). It was not necessary to let the reaction proceed for a long time, since after 5 minutes, the yield did not improve (Figure 4). This is advantageous in radiopharmaceutical synthesis, even if, with the 64-h half-life of yttrium-90, this is not crucial. For comparison, Yu *et al.* (Yu et al., 2003) have chelated 8-hydroxyquinoline (oxine) with yttrium-90 to label Lipiodol. The ^{90}Y -oxine complex is prepared in 30 min at 50°C. As well, the covalent binding of Lipiodol and yttrium-90 via an *N,N,N',N'*-tetrakis (2-benzimidazolymethyl)-1,2-ethanediamine (EDTB) chelate (Wang et al., 1996b) necessitated a 4-hour preparation.

Several dithiocarbamates, with different chain lengths, were investigated to find the optimal complex to label Lipiodol. The optimised procedure (pH = 4.75, 5 min at room temperature) was used. There were no significant differences between two carbons (DEDC, **L1**) and twelve carbons, **L3**. All complexes were obtained in high yield. On the other hand, with the sixteen carbons alkyl chain **L4** ligand, labelling yield decreased to 62.95 ± 8.86 % (Figure 5), most likely due to steric hindrance. Indeed, stability of lanthanide dithiocarbamate complexes highly relies upon steric effects of the dithiocarbamate substituent (Siddall, III and Stewart, 1970). Increasing the reaction time with **L4** did not change the outcome.

This trend is confirmed when labelling Lipiodol with these complexes (Figure 6). Using the long-chain **L4** dithiocarbamate ligand, the labelling yield decreased to 64 %. This low yield was not due to poor extraction of the highly lipophilic complex, but because of the low formation of this compound, as most of the activity was free ^{90}Y . Labelling yield was also somewhat lower with $[^{90}\text{Y}(\text{L1})_3\text{Phen}]$ compared to $[^{90}\text{Y}(\text{L3})_3\text{Phen}]$, due to the lower lipophilicity of the complex. TLC profiles, on ITLC-SG plates in methanol, showed only one spot, thus indicating only one species in the organic phase. Comparison of TLC profiles for $[\text{Y}(\text{DEDC})_3(\text{Phen})]$, both prepared at macromolecular scale (characterised by NMR and electrospray mass analysis) and at tracer level, confirmed the chemical identity of the radiotracer ($R_f = 0.76$).

Labelling Lipiodol with $[^{90}\text{Y}(\text{dtc})_3\text{Phen}]$ is easy and consists more precisely in an extraction of the yttrium complex into the Lipiodol phase (Mu et al., 2007). Selective extraction was attained with 5-minute shaking at room temperature, without the need for intermediate organic solvent extraction and subsequent evaporation, as was the case for the oxine complexes, which required an extraction into dichloromethane prior to solubilisation in Lipiodol (Yu et al., 2003; Das et al., 2009; Subramanian et al., 2010).

In vitro stability has been checked in saline, over a period of 8 days (Figure 7). Here, $[^{90}\text{Y}(\text{L1})_3\text{Phen}]$ appeared to be more stable than $[^{90}\text{Y}(\text{L3})_3\text{Phen}]$. Indeed, the latter complex was more easily released from Lipiodol, this release increasing with time, while 80 % of the activity remains in Lipiodol with $[^{90}\text{Y}(\text{L1})_3\text{Phen}]$.

4- Conclusions

A new method for the ^{90}Y -labelling of Lipiodol has been demonstrated. Based on labelling yields and *in vitro* stability, [$^{90}\text{Y}(\text{DEDC})_3(\text{Phen})$] seems to be the best candidate. Animal experiments are underway to check the biodistribution profile and *in vivo* stability of the radioconjugate. Lipiodol labelling with stronger activities (therapeutic doses) of yttrium-90 is also envisaged, to ascertain potential autoradiolysis. For this, automation of the synthesis is planned.

Abbreviations

Bipy = 2,2'-bipyridyl

DEDC = diethyldithiocarbamate

dtc = dithiocarbamate

HCC = hepatocellular carcinoma

Phen = 1,10-phenanthroline

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Figure 1: Structure of the mixed ligand yttrium complexes $[Y(dtc)_3(Phen)]$

Figure 2: Influence of the pH on the radiosynthesis of $[^{90}Y(L1)_3Phen]$

Figure 3: Influence of the temperature on the radiosynthesis of $[^{90}Y(L1)_3Phen]$

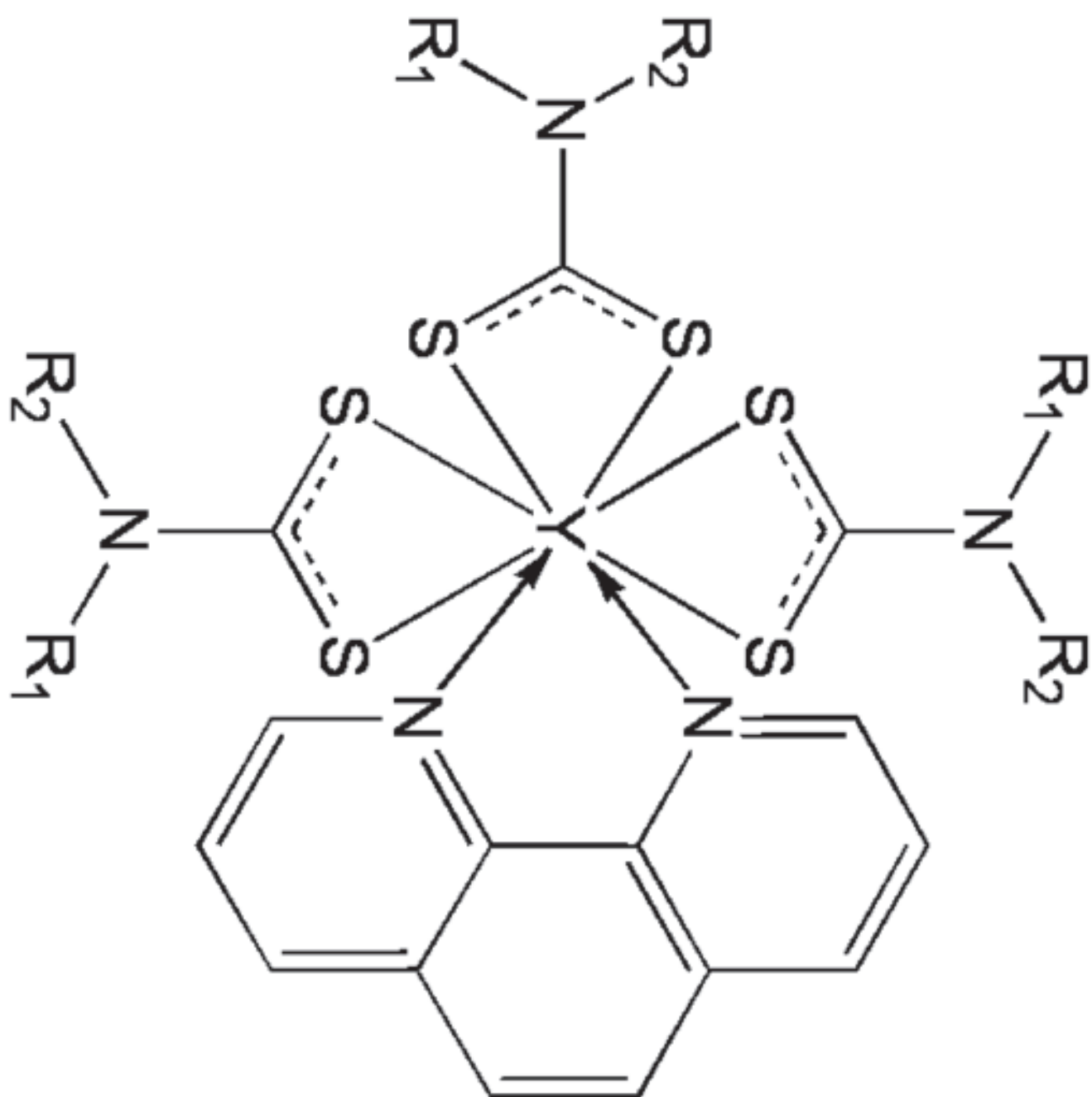
Figure 4: Influence of the reaction time on the radiosynthesis of $[^{90}Y(L1)_3Phen]$

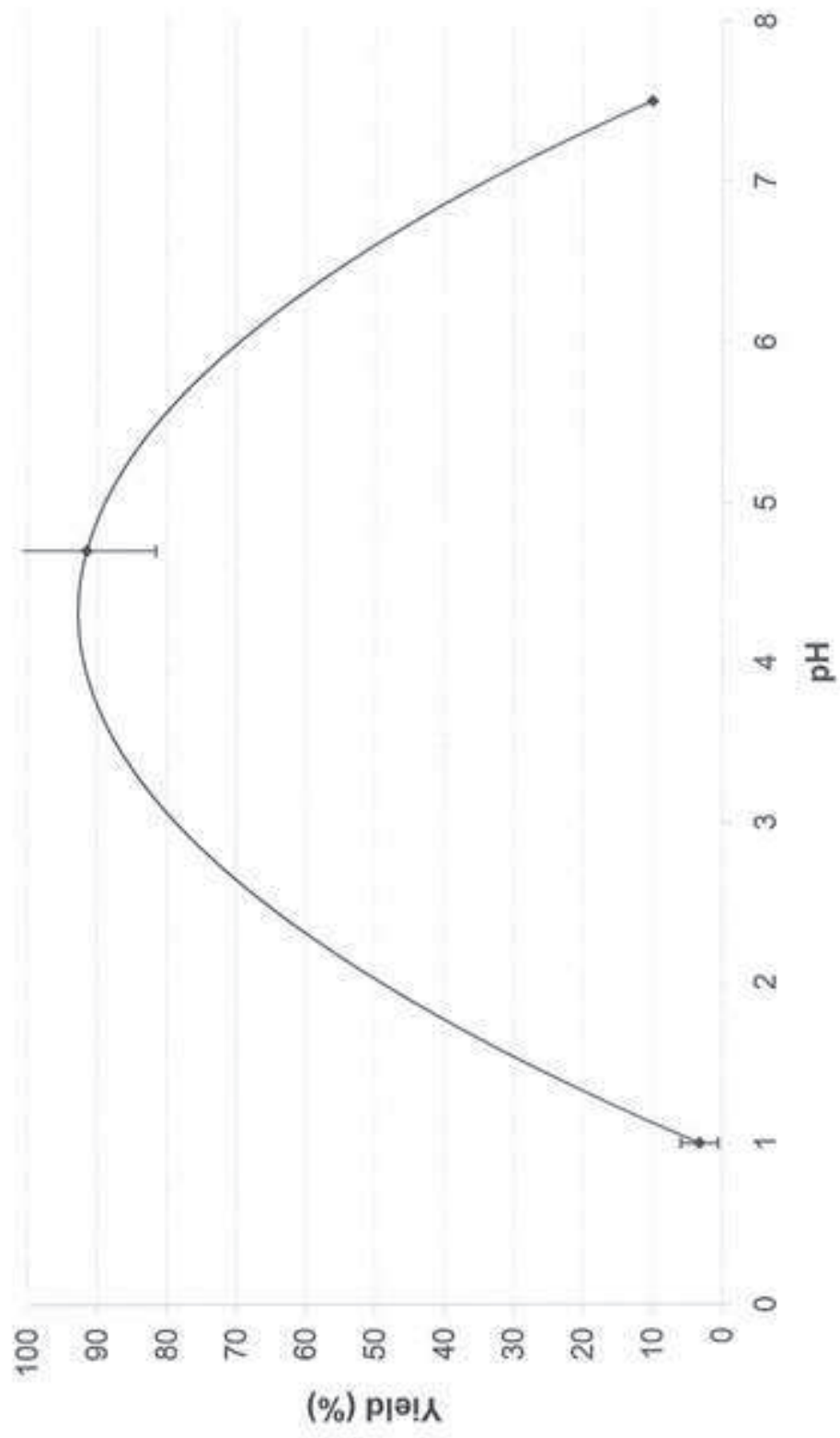
Figure 5: Influence of the alkyl chain length on the radiosynthesis (5 min, RT)

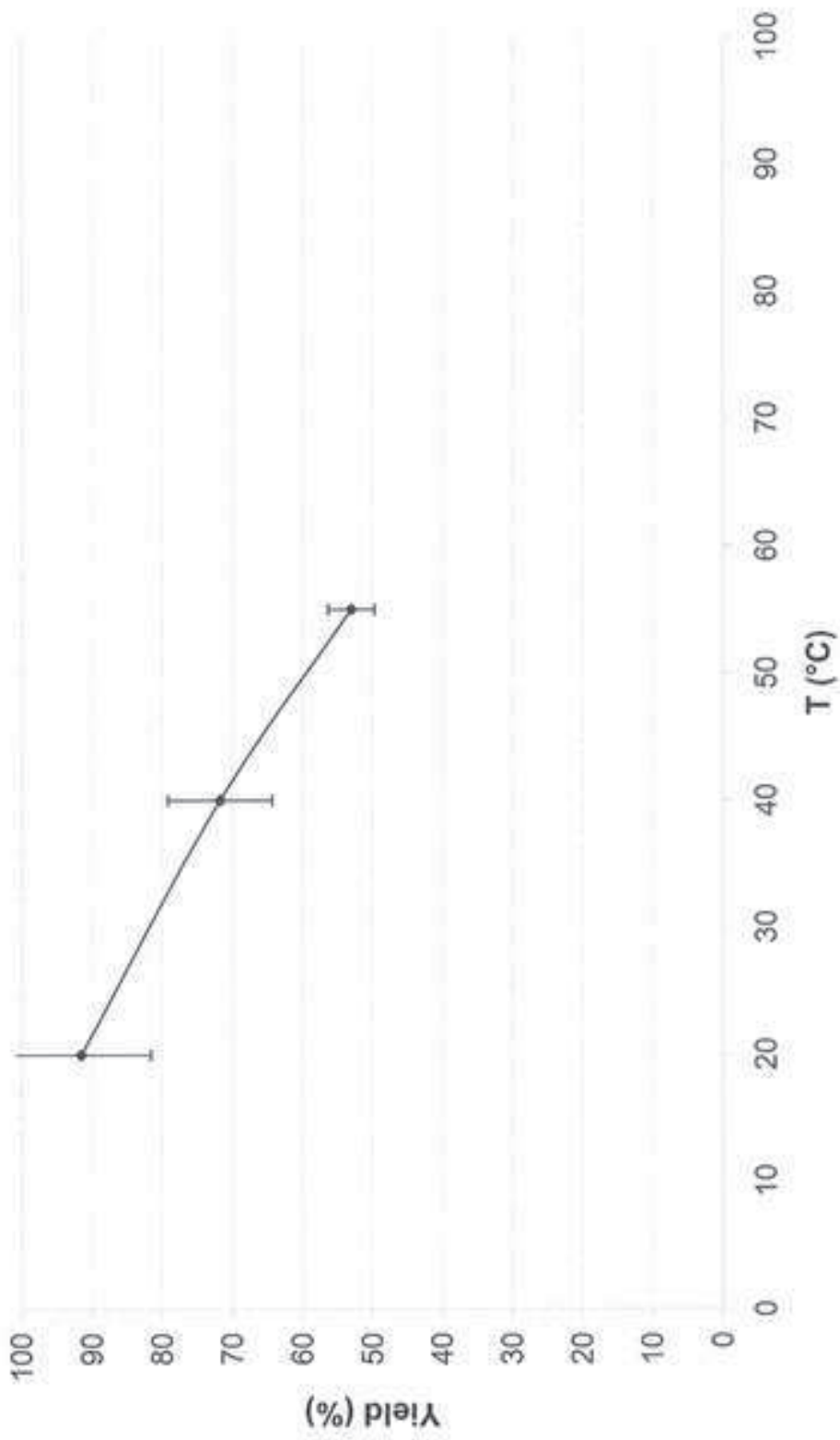
Figure 6: Influence of the alkyl chain length on the radiolabelling of Lipiodol (5 min, RT)

Figure 7: In vitro stability of the radiotracers $[^{90}Y(L1)_3Phen]$ and $[^{90}Y(L3)_3Phen]$

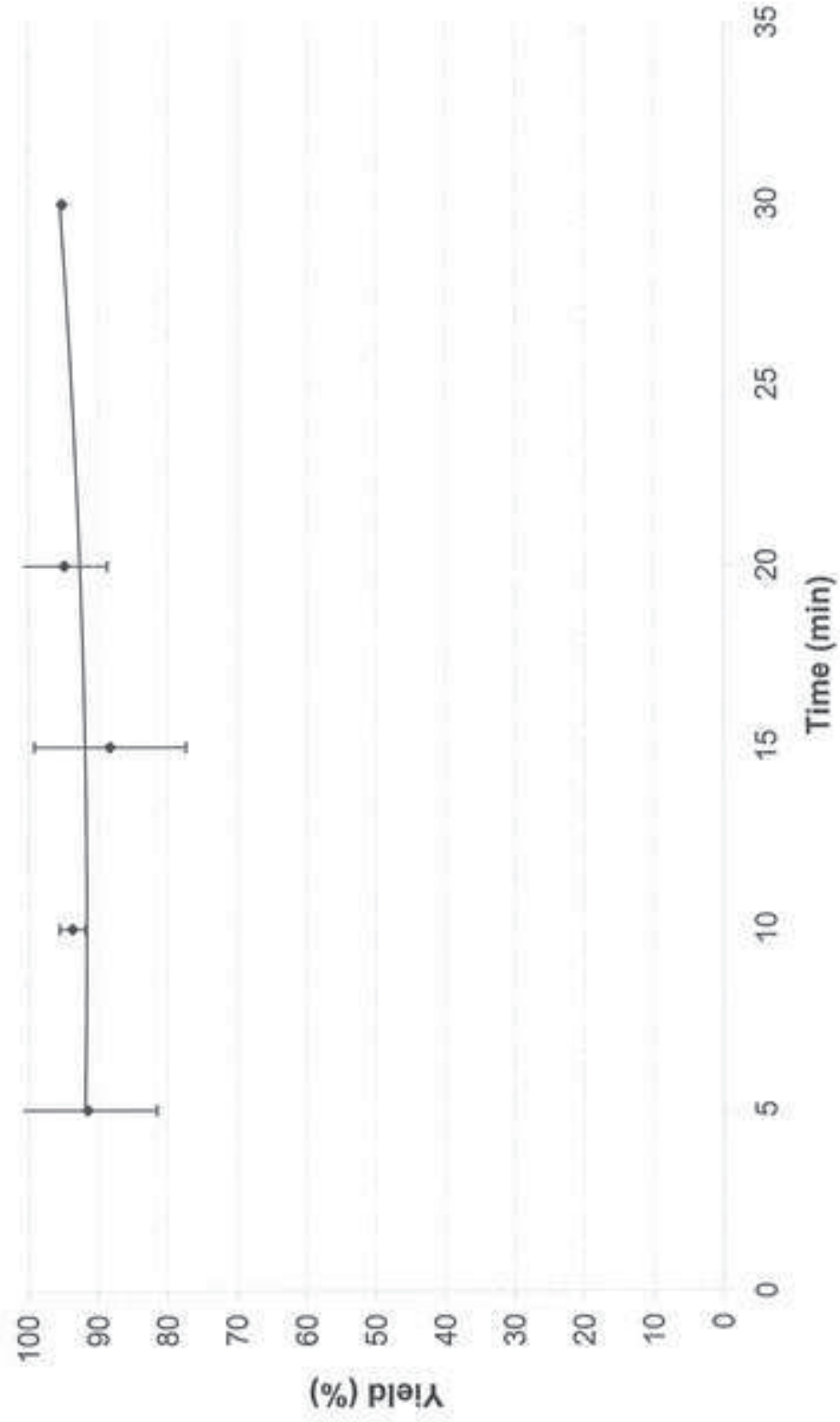
Table 1: The different ligands studied for the preparation of yttrium complexes



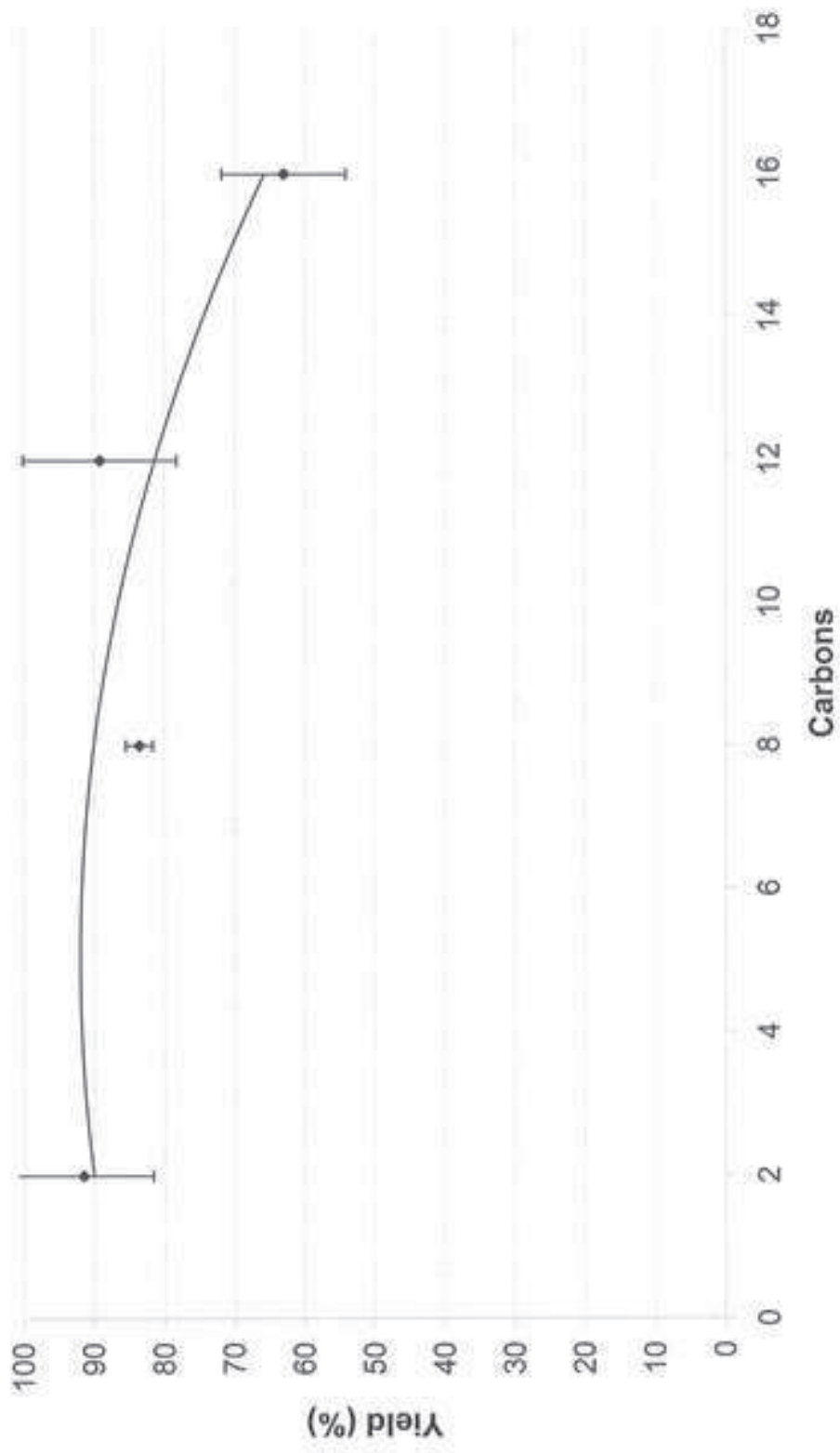




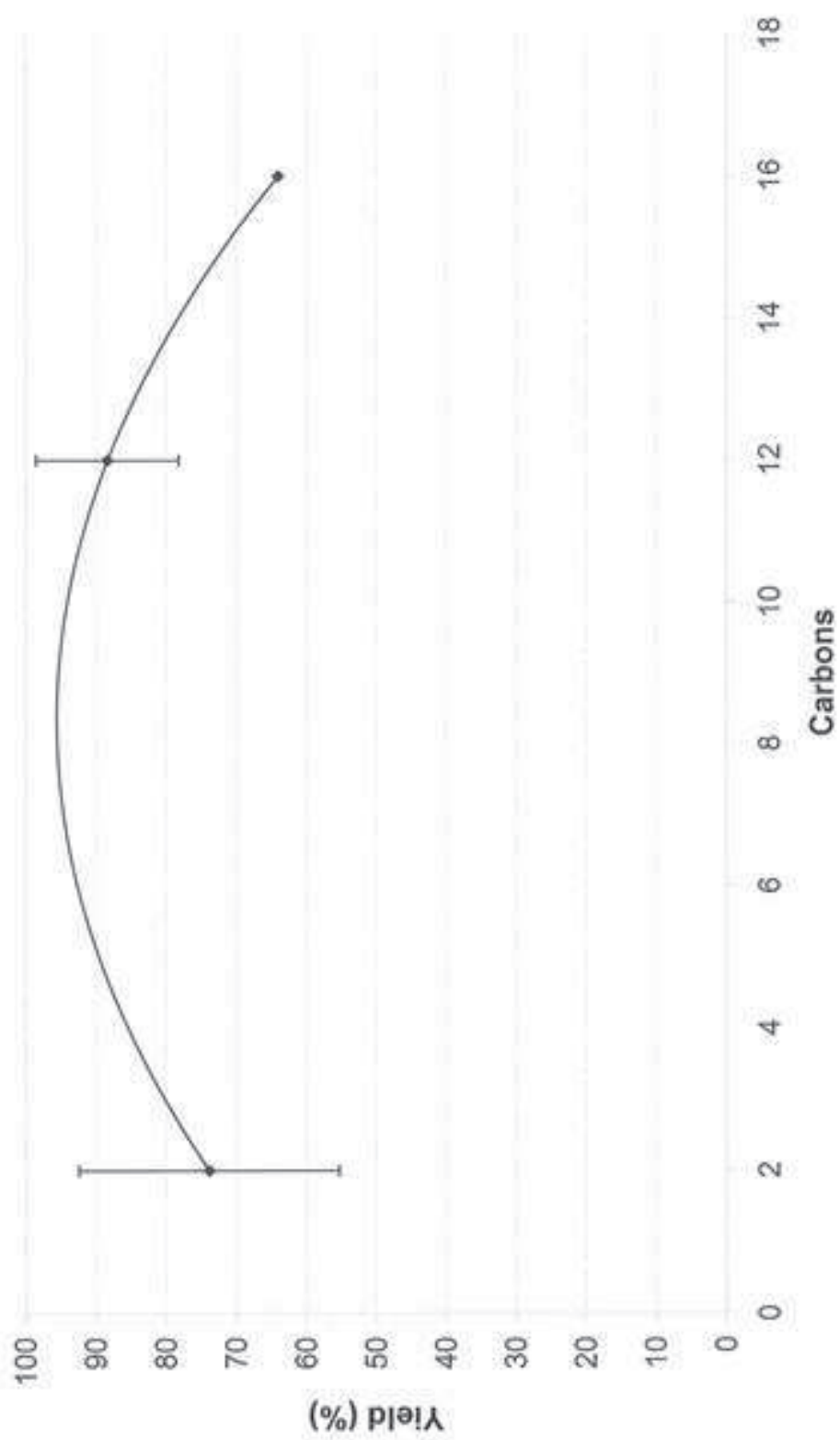
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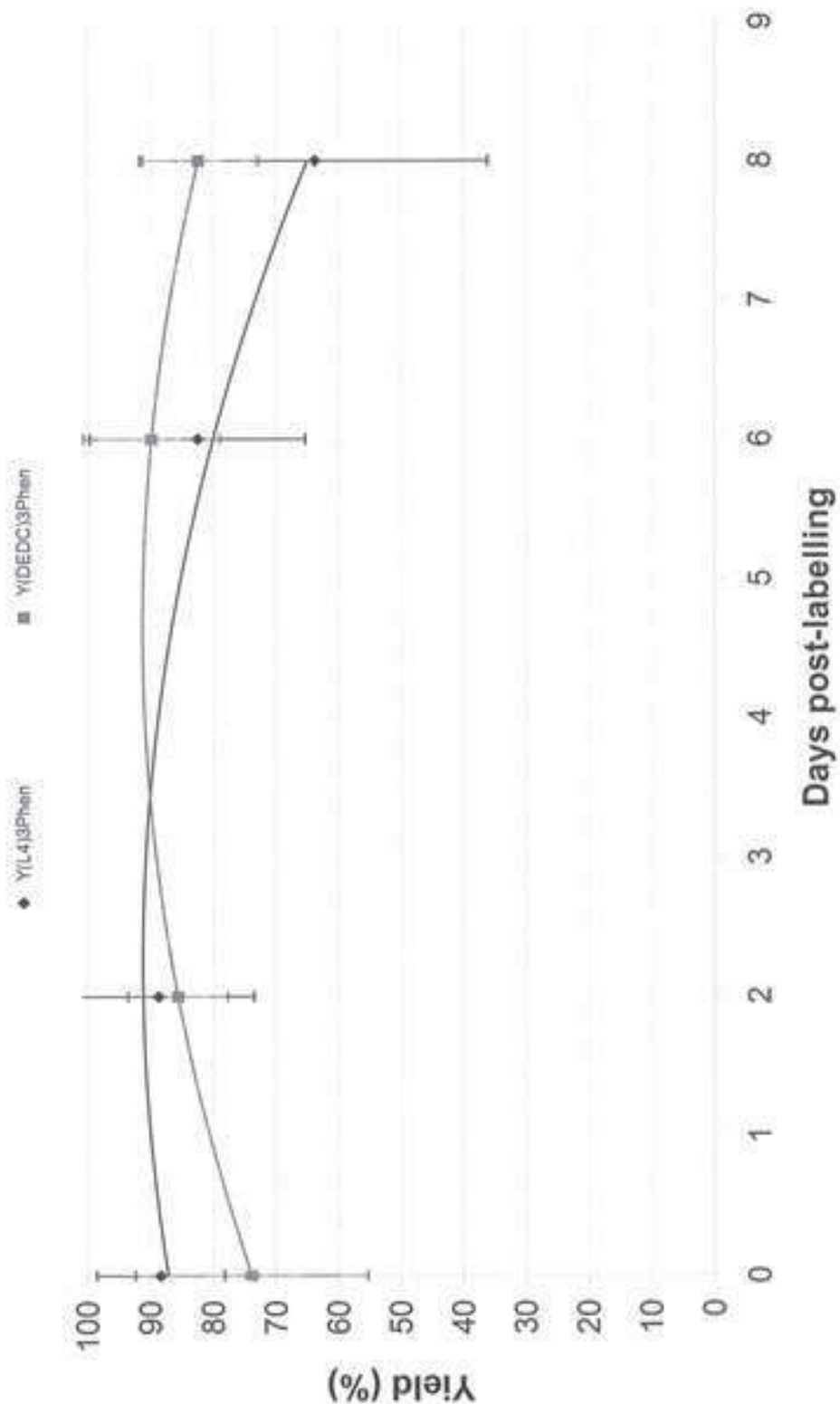


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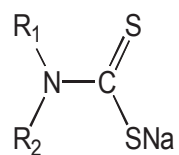


Figure





Figure



R_1	R_2	<i>Ligand</i>
Et	Et	L1
CH ₃ (CH ₂) ₇	Me	L2
CH ₃ (CH ₂) ₁₁	Me	L3
CH ₃ (CH ₂) ₁₅	Me	L4